Announcing a viral aetiology of MS has been an occupational hazard of neurological research for several decades. The geographical distribution and epidemiology of MS is consistent with the notion of exposure to a transmissible agent. MS could be a rare outcome of a relatively common infection, possibly resulting from immunological cross-reaction between antigens of the pathogen and of myelin-producing cells. Such autoimmune neuropathology could be triggered by a 'hit-and-run' virus that does not persist in the MS patient, but most investigators have searched for evidence of a persistent infection.

Viruses have been sought by three main methods: serology, isolation and antigen or genome detection. Serology has the advantage of being suitable for the study of large numbers of samples. If the suspect is a known virus, existing serological assays can be employed to search for an association with MS. But if the virus is a ubiquitous one, the association becomes difficult, as it cannot then be distinguished by the presence vs absence of antibodies but rather from raised titres or differential titres between serum and cerebrospinal fluid. If one suspects a new virus then it must first be isolated in order to devise a serological test, unless one relies on cross-reacting antibodies to other related viruses, for which the tests will by definition be less specific.

The precision of molecular techniques for detecting viral genomes should have provided a better resolution of virus candidates for MS. But it seems to have led to even greater confusion, especially with the introduction of the polymerase chain reaction (PCR) for genome amplification. Whereas neurologists were already well educated about spurious immunological cross-reactions, reports of amplified viral genomes were published uncritically, with insufficient debate about the possibility of the false positives they really proved to be. Authors pushed forward the most favourable interpretation either out of enthusiasm or from a desire to win their next grant or to boost investment of the biotechnology company in which they had an interest. So the literature is littered with articles that are best left uncited.

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Three groups of viruses have attracted interest in relation to MS: morbilliviruses, herpesviruses and retroviruses.

Morbilliviruses are a cause of MS in vogue for several years when debate swung between variants of measles virus or of canine distemper virus. However, morbillivirus genomes were not detected, so an acute, non-persistent infection was invoked, in contrast to the presence of defective yet abundant measles virus genomes in the brain of patients suffering from subacute sclerosing panencephalitis. The evidence for morbillivirus involvement in MS over the last decade, however, has not strengthened.

Herpesviruses attracted attention because they establish persistent infections, as well as being neurotropic. Viruses such as herpes simplex type 1 (HSV-1) and varicella zoster virus are naturally latent in the sensory ganglia of healthy individuals, and HSV-1 can also cause encephalitis. The discoveries during the last 10 years of three new human herpesviruses, HHV-6, HHV-7 and HHV-8, emphasize the fact that further as yet unknown viruses may be awaiting discovery.

HHV-6 was first described in AIDS-related Kaposi’s sarcoma (KS) in December 1994 and may be causally linked to KS. Therefore it is also known as KS-associated herpesvirus (KSHV). This virus has not yet been isolated and propagated in vitro. It was discovered through a powerful new method of subtractive DNA hybridization employing PCR amplification steps known as representational difference analysis (RDA). Only a part of the viral genome has been cloned and sequenced to date. RDA has recently been applied to comparisons of MS brain tissue and normal brain, and yielded sequences that represent HHV-6. HHV-6 was also first isolated from AIDS patients, but is actually present in the great majority of adults. In our view, it may be a passenger in the MS brain because it is T-lymphotropic as well as neurotropic and there are far more T cells in brain tissue with MS pathology than in unaffected brain tissue.

Another almost ubiquitous herpesvirus is Epstein-Barr virus (EBV). Two papers in this issue link EBV to MS. Munch et al. in Aarhus describe EBV-transformed lymphoblastoid cell lines producing both EBV and a retrovirus-like particle from five MS patients. More interestingly, the same group (Haahr et al.) report an increased risk of MS after late EBV infection which typically causes infectious mononucleosis (IM; mono). A historical prospective analysis suggests almost a 3-fold increased relative risk of MS following IM. Thus, the authors propose that, while EBV is unlikely to be a primary cause of MS, IM could be a co-factor in its development.

Retroviruses represent another virus family that comes in and out of fashion as a cause of MS. Retroviral genomes integrate into chromosomal DNA and persist for a lifetime or longer – they can be vertically transmitted. Animal and human retroviruses are known to cause CNS disease. For example, a minor variant of the envelope glycoprotein of a strain of mouse leukaemia virus causes a form of motor neuron disease, and others are linked to a variety of autoimmune syndromes. The human T-cell leukaemia virus type I (HTLV-I) not only causes adult T-cell leukaemia-lymphoma in about 3% of infected individuals, but has also been shown to cause tropical spastic paraparesis (TSP), a disease first described in
Jamaica, where HTLV-I infection is endemic. In Japan, where HTLV-I is also widespread, TSP is called HTLV-associated myopathy (HAM). HTLV-II, a distinct though related retrovirus, is endemic in many groups of native American Indians and in some Africans (e.g. pygmies), and is epidemic among intravenous drug users. The pathogenesis of HTLV-II is less well defined, but there is growing evidence linking it with neurological disorders.

It was obvious, therefore, to look for evidence of infection by HTLV-related viruses in MS and to search for such viruses in populations in which MS is most prevalent. Some antigenic cross-reactions with viral p19 (matrix) and tax (transactivating) proteins were recorded, as were claims to detect HTLV-related genome sequences. If these findings had real substance, the related genes should by now have been cloned and properly characterized.

There is no reason to think that HTLV-I and -II and HIV-1 and -2 are the only human retroviruses; more may await discovery. The presence in normal human DNA of thousands of endogenous, 'fossil' retroviral genomes may obscure the picture. Most of these genomes are defective, but a few have functional genes that can be expressed as proteins and sometimes produce whole virus particles. The puzzle is to determine whether such endogenous retrovirus expression is etiologically related to the syndromes in which they are observed, whether they are consequences of the syndrome (and hence may be useful markers of disease) or whether they are also expressed by the same cell types in healthy individuals. Rasmussen et al. in this issue have probed the expression of three specific human endogenous retroviral genomes in the peripheral blood of mononuclear cells of MS patients. They find no significant difference in retroviral expression from that in peripheral blood mononuclear cells of healthy, control subjects.

Retrovirus expression can also be detected by the tell-tale enzyme of retroviral particles, reverse transcriptase. In inexpert hands, however, the enzyme assay is fraught with difficulty, usually false-positive results, as cellular DNA polymerases will utilize RNA templates under certain in vitro conditions. One such cautionary tale is related by Froussard in this issue, who shows that a putative retrovirus isolated from a MS patient is in fact mycoplasma associated.

Overall, there are good reasons for continuing to search for viruses (and other microbes) that might be etiologically linked to MS. But each report needs to be examined critically, and the field would benefit from a greater exercise of self-restraint and quiet, steady, thorough research before rushing into print or to the microphone.